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THE CONTRIBUTION OF MALARIA IN PREGNANCY TO PERINATAL MORTALITY

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Abstract. The link between malaria and perinatal mortality was explored by systematically reviewing 117 studies published between 1948 and 2002. The mean perinatal mortality rate was higher in malaria endemic countries (61.1/1,000, 95% confidence interval [CI] = 52.1–70.1) than in non-endemic countries (25.8/1,000, 95% CI = 21.1–30.6). Similarly, the fetal mortality rate was higher in endemic countries (40.1/1,000, 95% CI = 32.1–48.0) than in non-endemic countries (20.0/1,000, 95% CI = 13.2–26.8) countries. Considering that perinatal mortality is an important indicator of obstetric care quality and socioeconomic development, further analysis was restricted to countries with a human development index between 500 and 800. In this category, the perinatal mortality rate was also significantly higher in endemic countries (50.5/1,000, 95% CI = 35.5–65.5) than in non-endemic countries (30.0/1,000, 95% CI = 25.7–34.3). In some publications, the occurrence of placental malaria and stillbirth was available. Placental malaria was significantly associated with a higher risk for stillbirth, regardless of parity (odds ratio = 2.19, 95% CI = 1.49–3.22, $P < 0.001$). Despite the limitations involved in this kind of review, all information found indicates that in endemic countries, malaria is an important determinant of perinatal mortality. Preventive measures such as intermittent preventive treatment or insecticide-treated bed nets could substantially reduce perinatal mortality and fetal wastage.

INTRODUCTION

Perinatal mortality is an important indicator of obstetric care quality and socioeconomic development.[1] Not surprisingly, the highest perinatal mortality rates (PMRs) are found in developing countries, particularly in Africa. Few studies have simultaneously considered intra-partum morbidity, sociodemographic factors, and diseases such as infection with human immunodeficiency virus, malaria, and malnutrition as risk factors for perinatal mortality. The proportion of perinatal deaths attributable to them is not well known.[2] It is widely recognized that malaria has a negative effect on the outcome of pregnancy. Pregnant women with little or no pre-existing immunity are at high risk of cerebral malaria, hypoglycemia, pulmonary edema, and severe hemolytic anemia, and fetal and perinatal loss can be as high as 60–70%.[3–6] The link between malaria and perinatal morbidity/mortality is less clear in areas with stable endemic malaria where pregnant women have acquired immunity. Malaria infection can cause maternal anemia, low birth weight (LBW), and possibly abortion and stillbirth.[7] The mean birth weight of infants born by mothers with placental malaria is reduced by 55–310 grams.[8–15] Low birth weight is more frequent in primigravidae with placental malaria compared with those without placental malaria (Kortmann HF, 1972. *Malaria and Pregnancy*. MD Thesis. Utrecht, The Netherlands: Drukkerij Elinkwijk).[9,10,14] Placental malaria is responsible for up to 35% of preventable LBW in malaria-endemic areas.[16] In malaria-endemic African countries, at least 13% of all infant deaths can be attributed to LBW resulting in 62,000–363,000 infant deaths per year.[17,18] A recent review analyzing the malaria population attributable risk for anemia (3–15%), LBW (8–14%), and infant mortality (3–8%) estimated that each year between 75,000 and 200,000 infant deaths are associated with malaria infection in pregnancy.[19] Perinatal mortality caused by malaria is estimated to be 25–80/1,000/year, although several studies have failed to show a clear and significant relationship.[20–22] The aim of this report is to determine the contribution of malaria to perinatal mortality by systematically reviewing relevant published data.

METHODS

Case definition. The definition of perinatal mortality and stillbirth used in this review is that recommended by the World Health Organization (WHO) Maternal Health and Safe Motherhood Program (WHO/FRH/MSM/96.7) and is based on the International Classification of Diseases, revision 10 (ICD-10). Fetal death is defined as death prior to the complete expulsion or extraction of the product of conception, irrespective of the duration of pregnancy. Fetal mortality rate (FMR) is the number of fetal deaths in a year divided by the total number of life births and fetal deaths in a year × 1,000. Stillbirth (late fetal death) is defined as death of a fetus of ≥28 weeks gestation. Early neonatal death is the death of an infant within the first seven days of life. Perinatal deaths include late fetal and early neonatal deaths. The PMR is the number of perinatal deaths divided by the number live births in a year × 1,000 (Figure 1).

Since the PMR is clearly linked to poverty and might confound the relationship between malaria and PMR/FMR, we used the Human Development Index (HDI) as an indicator. The HDI is a summary of three components: long and healthy life, knowledge, and a decent standard of living. It is computed by combining a life expectancy index, an education index based on the adult literacy rate and the combined primary, secondary, and tertiary education gross enrollment ratio, and the Gross Domestic Product (GDP) index based on the GDP per capita.[23] The HDI is stratified into three categories following the United Nations Development Program classification: low (HDI < 500), medium (500 ≤ HDI < 800), and high (HDI ≥ 800) human development.

Malaria-endemic areas are defined as areas with significant annual transmission, be it seasonal or perennial. Epidemic areas are defined as areas prone to distinct inter-annual variation, in some years with no transmission taking place at all.[24] When available in the recorded studies, the percentage of mothers infected with malaria (peripheral blood smear positive, placental blood smear positive) was used as a proxy marker of malaria endemicity. Placenta results are more sen-

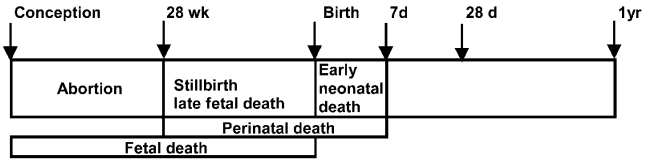

FIGURE 1. Terminology applied to fetal and infant intervals and events.[40] wk = weeks; d = days; yr = year.

sitive than peripheral blood for detecting maternal infection, and are more accurate in predicting fetal morbidity.[25] Values of malaria prevalence in Africa were obtained from the Mapping Malaria Risks in Africa database (http://www.mara.org.za).

Data sources. A literature search for data on perinatal mortality rate and stillbirth in developed and developing countries was undertaken. MEDLINE, CAB HEALTH, and Cochrane reviews were searched with combinations of the following keywords: perinatal mortality, stillbirth, pregnancy, developing countries, developed countries, malaria, and placenta. Theses known through professional contacts or found in the Institute of Tropical Medicine (Antwerp, Belgium) database were searched with the same keywords. Information on stillbirth outcome in relation to placental malaria was also searched. Reference lists of collected articles were checked for additional references. All data were categorized by location, source (hospital or community), parity, PMR, and stillbirth rate (FMR). Most studies included only singleton births (a few did not make a difference) and were usually not stratified and/or analyzed by parity.

For the meta-analysis quantifying the risk of delivering a stillbirth associated with placental malaria, a study was included if it had a clearly stated diagnostic method for detecting placental malaria. It should have also reported either the relative risks (or odds ratios) of stillbirth according to placental malaria or the raw data to allow these to be computed.

Statistical analysis. Two types of analysis (STATA version 8.0; Stata Corp., College Station, TX) were done: an ecologic and a meta-analysis. The PMR and FMR were computed against HDI in malaria-endemic countries and in non-endemic countries. Malaria endemicity and HDI were used as continuous and categorical variables. Correlation coefficients were calculated for the continuous variables. We also compared the HDI and PMR/FMR as a continuous variable between malaria-endemic countries and non-endemic countries. Mean PMR/FMR were compared between the different categories (low, medium, and high HDI; endemic and non-endemic malaria). The relationship between FMR and the prevalence of placental malaria was explored by using data from publications where both variables were reported.

Studies that reported the risk of stillbirths in women (all parities) with a positive and a negative placental blood smear were used for the meta-analysis. The random effects meta-analysis model was used to calculate pooled odd ratios (ORs) and 95% confidence intervals (CIs). A random effects model was used as it assumes a different underlying effect for each study.[26,27]

RESULTS

For the ecologic analysis**,** 117 studies published between 1948 and 2002 were found. The PMR and/or FMR were obtained mostly from hospital records. The mean PMR was higher in 36 studies from endemic countries (61.1/1,000, 95% CI = 52.1–70.1) than in 59 studies from non-endemic countries (25.8/1,000, 95% CI = 21.1– 30.6). Similarly, the FMR was higher in 40 studies from endemic countries (40.1/1,000, 95% CI = 32.1–48.0) than in 42 studies from non-endemic countries (20/1,000, 95% CI = 13.2–26.8). When plotting PMR against HDI, PMR increased with decreasing HDI, and the highest values were found in countries with the lowest HDI (Figure 2). However, considering that few non-endemic countries had HDI values <500 and no endemic country had an HDI value >800, a meaningful comparison was possible only for countries with an HDI between 500 and 800. In this category, the PMR was significantly higher in endemic countries (50.5, 1,000, 95% CI = 35.5–65.5) than in non-endemic countries (30/1,000, 95% CI = 25.7–34.3). In endemic countries, no obvious linear trend between PMR and parasite prevalence was found.

Twenty-five publications from Africa published between 1948 and 2002 and where malaria was specifically reported as a cause of perinatal death and/or stillbirth were found. Approximately two-thirds (68%) were based on hospital data and approximately half (48%) were from urban areas. The PMR ranged from 24/1,000 to 137/1,000, the FMR ranged from 2.3/1,000 to 111/1,000, and placental malaria ranged from 6% to 64% (Table 1). Within the African continent, no significant differences between the different regions (all of them belonging to low HDI countries) was found.

Eleven additional studies from others continents and published between 1951 and 2000 were found. We analyzed these separately because the study conditions were different from those in Africa. Three of them reported perinatal mortality and stillbirth during an epidemic and were excluded from analysis. More than two-thirds (75%) of these publications were based on hospital data and were from rural areas. The PMR was mentioned in only two studies, the FMR ranged from 12/1,000 to 27/1,000, and placental malaria (blood smear) ranged from 4% to 55% (Table 2). The association between FMR and the prevalence of placental infection was not significant (R = 0.59, $P = 0.12$). The association between

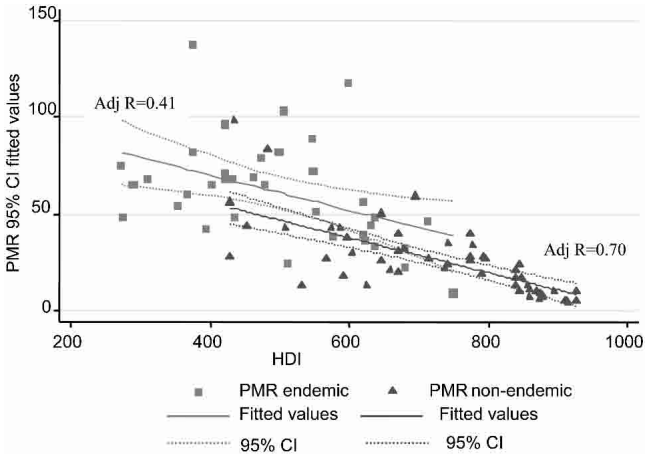

FIGURE 2. Perinatal mortality rate (PMR) by human development index (HDI) as a function of the malaria endemicity (55 studies in non-endemic countries and 34 in endemic countries; there are four missing values for the HDI). Adj. = adjusted; CI = confidence interval.

TABLE 1
Malaria reported as a cause of perinatal death (including stillbirths) in Africa*

Country	Year	Data source	Study site	No. of births	PG (%)	LBW (%)	PD	PMR (%)	PM (%)	Stillbirths	FMR (%)	Reference
Central African Republic	1986	H	–	101	–	–	–	–	64	7	69	42
Democratic Republic of the Congo	1948	H	U	403	–	–	27	68	60	–	–	39
Ghana	2001	H	R	5,887	33	20	424	72	–	–	–	43
Guinée-Bissau	1997	H	U	202	29	26	–	–	14	21	104	44
Kenya	1975–1976	C	R	2,246	20	–	105	47	0.2	67	30	45
Malawi	1995–1996	C	R	796	24	15	52	65	30	36	45	46
Malawi	1987–1989	H	R	2,063	36	18	111	54	21	65	29	47
Nigeria	2002	H	U	564	27	–	–	–	25	16	28	48
Nigeria	1986	H	U	105	20	11	–	–	6	6	57	49
Sierra Léone	1987–1991	H	U	68,883	–	17	3,280	48	–	2,564	39	50
Sudan	1983	C	U	213	–	–	9	42	–	5	24	51
Tanzania	1997–1998	RC	RC	679	–	22	–	–	61	31	46	52
Tanzania	1989–1990	H	U	440	25	5	–	–	21	1	2	53
Tanzania	1989–1991	C	R	427	–	10	29	68	–	12	28	54
Tanzania	1989–1990	H	U	3,174	–	15	304	96	–	245	77	62
The Gambia	1997	H	R	313	31	24	43	137	52	35	111	55
The Gambia	1966–1972	H	U	2,927	44	–	–	–	12	–	47	4
The Gambia	1966–1972	HC	R	3,500	26	–	–	–	27	–	79	4
The Gambia	1982–1983	C	R	658	–	–	49	75	8	23	35	56
The Gambia	1991–1992	C	R	462	100	13	–	82	33	27	57	29
Uganda	1997–1998	H	R	3,212	40	14	–	–	34	63	20	57
Uganda	1997–1998	H	R	2,779	43	5	–	–	81	192	69	57
Uganda	1998	H	U	537	29	11	–	–	7	23	43	58
Zaire	1989–1990	H	R	297	25	10	7	24	33	4	13	25
Zaire	1980–1984	H	U	49,681	34	–	–	–	18	1,535	31	59

* PG = primigravidae; LBW = low birth weight; PD = perinatal deaths; PMR = perinatal mortality rate; PM = placental malaria; FMR = fetal mortality rate; H = hospital; U = urban; R = rural; C = community; RC = refugee camp; HC = health center. Countries appearing more than once with the same reference number indicate that data from more than one study location are reported in the same publication.

PMR and placental malaria could not be explored because there were few data available.

Meta-analysis. Nine studies filled the criteria and corresponded to 11 records (Table 3). Placental malaria was significantly associated with a higher risk for stillbirth regardless of parity (OR = 2.19, 95% CI = 1.49–3.22; $P < 0.001$) (Figure 3).

DISCUSSION

The link between socioeconomic variables and childhood or infant mortality is well known and any attempt of investigating the contribution of malaria to perinatal mortality should take this into account.[28] The HDI, a summary estimate of several factors such as the life expectancy, education, and the GDP, was used as a rough measure of the socioeconomic status at the country level. Not surprisingly, the PMR and FMR were strongly correlated with HDI. Moreover, most of the malaria-endemic countries had an HDI <800 and many of them clustered around the lowest HDI values. This means that despite the higher values for the PMR and FMR in developing countries, it is extremely difficult to attribute this difference to the presence of malaria. We have tried to circumvent this problem by analyzing only countries with an HDI between 500 and 800 and found that the PMR was significantly higher in endemic countries than in non-endemic countries. Again, these results should be taken with caution for several reasons. First, the HDI reflects the present socioeconomic situation while the PMR and FMR data have been extracted from articles published over the past 50 years. Therefore, the HDI might not reflect the national economic development at the time the data were collected. Second,

TABLE 2
Malaria reported as a cause of perinatal death (including stillbirths) outside Africa*

Country	Year	Data source	Study site	No. of births	PG (%)	LBW (%)	PD	PMR	Malaria deaths (%)	P.f. (%)	Stillbirths	FMR	Reference
India	1997–1998	C	R	274	28	–	–	–	–	55	5	18	60
Thailand	1992–2000	H	R	386	30	19	–	–	–	100†	7	18	61
Thailand	1991–1994	H	R	3,587	24	15	–	–	–	31	61	19	62
Papua New Guinea	1987–1992	H	U	22,405	–	10	–	–	–	–	427	19	63
Papua New Guinea	1995–1997	H	U	–	–	–	–	–	–	15	315	22	64
India	2000	C	R	209	20	–	8	38	63	12	6	29	65
French Guyana	1992–1995	H	R	3,788	39	–	–	22	11	4	45	12	66
Thailand	1993–1996	H	R	1,567	–	16	–	–	–	37	43	27	67

* PG = primigravidae; LBW = low birth weight; PD = perinatal deaths; PMR = perinatal mortality rate; P.f. = *Plasmodium falciparum* infection; FMR = fetal mortality rate; C = community; R = rural; H = hospital; U = urban.
† Only *P. falciparum* positive were selected.

TABLE 3
Placental malaria and stillbirths (all hospital studies)*

Country	Year	Stillbirths† (PM/N)	Live births (PM/N)	OR	95% CI	Reference
Sierra Leone	1925	10/14	51/144	4.56	1.36–15.27	7
The Gambia	1983	22/138	330/2,789	1.41	0.88–2.26	4
The Gambia	1983	82/276	866/3,224	1.15	0.88–1.51	4
Gabon	1984	1/15	2/52	1.79	0.15–21.17	68
Gabon	1984	4/7	71/241	3.19	0.70–14.63	68
Vanuatu	1986	2/5	8/176	14.0	2.04–95.94	69
Sudan	1993	53/151	185/620	1.27	0.87–1.85	70
Mozambique‡	1995	11/58	7/58	1.71	0.61–4.76	71
Ethiopia	2003	0/2	12/183	–	–	72
Ethiopia	2003	4/26	17/807	8.45	2.63–27.19	72
The Gambia§	2002	25/35	135/278	2.65	1.23–5.72	55
Uganda	2000	5/23	34/514	3.92	1.37–11.21	58

* PM/N = placenta malaria/total number of stillbirths or live births; OR = odds ratio; CI = confidence interval. Countries that appear twice with the same study references indicates that within the study discreet and different distinct study sites have been analyzed.
† Stillbirths with known causes, such as cephalopelvic disproportion or uterine rupture, were excluded from the analysis.
‡ Cases and controls matched by age and parity.
§ Fresh and macerated stillbirths.

most of the publications reported data from hospital records and this might have introduced an important bias in the estimation of the PMR and FMR. Indeed, in many endemic countries, a large proportion of women does not deliver in hospitals, but rather in peripheral health centers or, more commonly, at home.[29] Therefore, the actual PMR and FMR are probably higher because a large percentage of perinatal deaths or stillbirths goes unreported. This is more likely to be true in countries with the lowest HDI, which are also those with the highest PMR values, than in countries with a medium or high HDI, since access to health care is probably lower. Therefore, the PMR difference between endemic and non-endemic countries might be even larger. Moreover, malaria is a major obstacle to overall economic development; during the period 1965–1990, endemic countries had a growth penalty of more than 1% per year (compared with countries without malaria), even after considering the effects of economic policy and other factors influencing economic growth. The annual growth loss by malaria has been estimated as high as 1.3% points per year.[30] The PMR and FMR are often linked to the quality of clinical care[31,32] and of obstetric and neonatal services in tropical[33] as well as in European countries.[34] If one considers that health care quality is often linked to economic development,[34] malaria might also have an indirect effect on the PMR by slowing economic development and consequently reducing the provision of health services of acceptable quality.

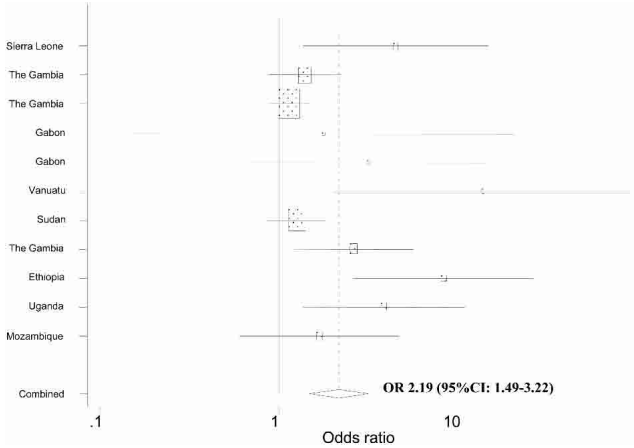

FIGURE 3. Effect of placental malaria on pregnancy outcome (stillbirths) by random effects meta-analysis. The sizes of the squares are directly proportional to the amount of information each study contributes to the meta-analysis. The diamond represents the effect of placental malaria in all studies, with the vertical axis of the diamond indicating the odds ratio (OR) and the span (horizontal axis) indicating the 95% confidence interval (CI).

We were unable to find any obvious trend between malaria prevalence and PMR. This is understandable when one considers that most of the publications reporting PMR values did not have any estimation of malaria prevalence, and that these had to be extracted from other studies done in the same country, but not necessarily in the same location, and during the same period. However, a meta-analysis (at individual level) showed that the stillbirth rate was strongly associated with placental malaria in endemic areas. The relationship between malaria and fetal loss has been described in low endemic or epidemic-prone areas,[35–38] but this is far from clear in highly endemic areas.[3,8,39] Therefore, we analyzed the individual risk of delivering a stillbirth according to the presence of placental malaria. A tendency of having a higher risk of delivering stillborn babies in women with placental malaria had been reported in all studies included in our meta-analysis, but in several of them such a link was not statistically significant. However, when pooled together, the risk of stillbirth was significantly higher in women with placental malaria. Several limitations ought to be mentioned. First, most of the data included in the meta-analysis came from hospital-based studies, i.e., from a selected group of women who decided to deliver in the hospital for a variety of reasons. These women might have had access to preventive measures, such as chemoprophylaxis, that would have decreased the risk of stillbirths. This would underestimate the impact of malaria on perinatal mortality. Alternatively, if one considers that women delivering at the health facilities might represent high-risk pregnancies, primigravidae for example, the impact of malaria on perinatal mortality might be overestimated. Community-based studies collecting information from all pregnant women would have given a better estimation and overcome selection bias, but they are extremely difficult to carry out. Second, in our analysis parity was not taken into account. Stratification

by parity might have shown a stronger effect in primigravidae compared with the other pregnant women because they are more vulnerable to malaria infection and placental malaria.[40] Moreover, most studies relied on the result of the placental smear whose sensitivity is low compared with placenta histopathology.[3] A more reliable method of assessing placental infection such as the histopathologic examination might have changed the results, although the delivery of a stillborn baby is probably linked to an active malaria infection that can also be detected by a placental smear.

In conclusion, despite the major limitations involved in this kind of review, all the information found indicates that in endemic countries, malaria is an important determinant of perinatal mortality. In the middle income countries (HDI between 500 and 800), a meaningful comparison was possible and we found that the PMR was significantly higher in endemic countries than in non-endemic countries. A meta-analysis of nine studies showed that placental malaria was associated with a more then two-fold risk for stillbirth, regardless of parity. This is consistent with the findings of a recent Cochrane review showing that malaria chemoprophylaxis significantly reduces PMN in primi- and secundigravidae.[41] Preventive measures such as intermittent preventive treatment or insecticide-treated bed nets could substantially decrease perinatal mortality and fetal wastage.[3]

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